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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/538,248	03/29/2000	David A. Cheresh	TSRI-651.3	6166

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EXAMINER
PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/538,248	Cheresh et al.
Examiner	**Art Unit**
Rebecca Prouty	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Mar 11, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) [X] The period for reply expires *6* months from the mailing date of the final rejection.

b) [ ] The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. [ ] A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. [ ] The proposed amendment(s) will not be entered because:

(a) [ ] they raise new issues that would require further consideration and/or search (see NOTE below);

(b) [ ] they raise the issue of new matter (see NOTE below);

(c) [ ] they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) [ ] they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. [ ] Applicant's reply has overcome the following rejection(s):

4. [ ] Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. [X] The a) [X] affidavit, b) [ ] exhibit, or c) [X] request for reconsideration has been considered but does NOT place the application in condition for allowance because:
see attached

6. [ ] The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. [X] For purposes of Appeal, the proposed amendment(s) a) [ ] will not be entered or b) [X] will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*

Claim(s) objected to: *none*

Claim(s) rejected: *1-4 and 16-20*

Claim(s) withdrawn from consideration: *5-15 and 21-31*

8. [ ] The proposed drawing correction filed on _____ is a) [ ] approved or b) [ ] disapproved by the Examiner.

9. [X] Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). *17*.

10. [ ] Other:

Applicant's arguments and the declaration by Dr. Cheresh et al. have been considered but are not persuasive to overcome the current rejections of the claims under 35 U.S.C. 103(a). Applicants argue that it would not have been obvious to one of ordinary skill in the art to treat tissue damage due to vascular edema because (1) there is no reasonable expectation of success that the inhibition of Src kinase would lead to inhibition of vascular edema or reduced tissue damage therefrom, (2) there are many pathways for activating Src kinase, and (3) different means of activating Src kinase lead to different downstream effects.

Applicants argument that there is no reasonable expectation of success that the inhibition of Src kinase would lead to inhibition of vascular edema or reduced tissue damage therefrom as Losordo et al., Hayashi et al., and Bao et al. each teach treatments of ischemia using VEGF and thus one would not expect inhibition of VEGF to be beneficial and as He et al. state that the post-receptor signaling pathways in general and the relationship between c-Src activation and the physiological effects of VEGF in particular is not well understood. However, each of Losordo et al., Hayashi et al., and Bao et al. teach treatment of ischemia (loss of blood flow) and not vascular edema (excessive accumulation of blood) with VEGF. While it is acknowledged that vascular edema is often a serious complication

of ischemia (presumably as a consequence of reperfusion after the constriction is removed) they are in fact opposite effects. As such one would not find the treatment of ischemia with VEGF to teach away from the treatment of vascular edema by inhibiting VEGF signaling. Furthermore, it is noted that ischemia is only one potential cause of edema. This is particularly noted by Hayashi et al. who state on page 892:

> "there exist many differences between brain edema associated with brain tumor and that associated with brain infarct. For example, dexamethasone is effective for reducing brain edema with brain tumor, but not for the treatment of ischemic brain edema (Fishman, 1982). On the other hand, dexamethasone inhibited VEGF gene expression and reduced the ability of VEGF to increase vascular permeability (Bruce et al., 1987). These data suggest that VEGF is not mainly involved in ischemic brain edema formation. In the relatively early phase, ischemic brain edema formation is mainly caused by cytotoxic edema rather than vasogenic edema (Betz and Coester, 1990)."

Therefore, at best the references only teach away from using inhibitors of VEGF signaling pathways for the treatment of ischemic induced edema. Applicants claims are clearly not so limited. Applicants arguments with regard to the statements of He et al. that the post-receptor signaling pathways in general and the relationship between c-Src activation and the physiological effects of VEGF in particular is not well understood is noted, however, knowledge of how VEGF induced c-Src activation leads to the known downstream effects of VEGF is not

necessary for the skilled artisan to have a reasonable expectation that if VEGF induced c-Src activation is inhibited, the downstream effects will be inhibited as well.

Applicants argue that there are many pathways for activating Src kinases and different means of activating Src kinase lead to different downstream effects. This is agreed with. However, the rejection has suggested inhibiting a known effect of one of these pathways (i.e., VEGF signaling) by inhibiting Src kinases. While the fact Src kinases can be activated by many other pathways may meant that inhibiting Src kinases could be used for other reasons as well it does not in any way suggest that inhibiting Src kinases would not also inhibit the downstream effects of VEGF and thus be reasonably expected to inhibit vascular edema.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652